

CLAIMS

1. A method of identifying a kinase or phosphatase that degrades insulin receptor substrate 1 (IRS-1) and  
5 reduces insulin-induced phosphorylation of protein kinase B (PKB) in an insulin-resistant cell, comprising the steps of:

a) transfecting a human hepatoma cell with short interfering ribonucleic acid (siRNA) against said kinase  
10 or phosphatase for a time and under conditions sufficient for said cell to incorporate said siRNA into its genome;

b) adding insulin to said resulting cell of step (a) for a time and under conditions sufficient for said cell to become insulin-resistant;

15 c) lysing said resulting cell of step (b) and separating resulting proteins;

d) determining IRS-1 protein level and phosphorylation of PKB, as compared to that of a cell transfected with control siRNA, an increased amount of  
20 IRS-1 and phosphorylated PKB, as compared to said cell transfected with control siRNA, indicating said kinase or phosphatase degrades IRS-1 and decreases phosphorylation of PKB in said insulin-resistant cell.

25 2. The method of claim 1 wherein said human hepatoma cell is a HepG2 cell.

3. The method of claim 1 wherein said identified kinase is selected from the group consisting of S6KB2,  
30 IKK2, PKC theta, pim 2, pyruvate dehydrogenase, PKC iota, PKC delta, UDP-N-acetylglucosamine-2-epimerimase/N-acetylmannosamine, CaMKI-like protein, DAPK2, casein kinase 1 delta, casein kinase 1 gamma 3, DCAMKL1, SnK

Akin kinase, NP\_067675, STK10, MAGUK p55 member 2, oxidative-stress responsiveness 1, NP\_060189, inositol 1, 3, 4 triphosphate 5-6 kinase, mitogen-activated protein kinase 4, mitogen-activated protein kinase 7, LIM kinase 2 (isoform 2b), phosphorylase kinase alpha 2, salt-inducible protein kinase, Jun kinase 1, 2, dystrophia myotonica protein kinase, CGPK1, MKK6, serine-threonine protein kinase PRP4 homolog, STE-2-like kinase, protein tyrosine kinase 9, P38 delta and adenylate kinase 3 (alpha-like).

4. The method of claim 1 wherein said phosphatase is PTEN.

5. The method of claim 1 wherein said determination of IRS-1 protein level and phosphorylation of PKB is performed by adding anti-IRS-1 and anti-phospho-PKB antibodies to said IRS-1 and phospho-PKB proteins for a time and under conditions sufficient for IRS-1/anti-IRS-1 antibody and phospho-PKB/anti-phospho-PKB antibody complexes to form and determining presence or absence of said complexes as compared to complexes formed from proteins of said cell transfected with control siRNA.

6. A kinase identified according to the method of claim 1.

7. A phosphatase identified according to the method of claim 1.

8. A method of treating a condition in a mammal characterized by diminished uptake and metabolism of glucose comprising the steps of administering to said mammal siRNA against a kinase or phosphatase, wherein  
5 said kinase is selected from the group consisting of S6KB2, IKK2, PKC theta, pim 2, pyruvate dehydrogenase, PKC iota, PKC delta, UDP-N-acetylglucosamine-2-epimerimase/N-acetylmannosamine, CaMKI-like protein, DAPK2, casein kinase 1 delta, casein kinase 1 gamma 3,  
10 DCAMKL1, SnK Akin kinase, NP\_067675, STK10, MAGUK p55 member 2, oxidative-stress responsiveness 1, NP\_060189, inositol 1, 3, 4 triphosphate 5-6 kinase, mitogen-activated protein kinase 4, mitogen-activated protein kinase 7, LIM kinase 2 (isoform 2b), phosphorylase kinase  
15 alpha 2, salt-inducible protein kinase, Jun kinase 1, 2, dystrophin myotonic protein kinase, CGPK1, MKK6, serine-threonine protein kinase PRP4 homolog, STE-2-like kinase, protein tyrosine kinase 9, P38 delta and adenylate kinase 3 (alpha-like) and said phosphatase is PTEN, in an amount  
20 sufficient to effect said treatment.

9. The method of claim 8 wherein said mammal is selected from the group consisting of a human, a domesticated animal and a non-domesticated animal.

10. The method of claim 8 wherein said condition is diabetes.

11. The method of claim 10 wherein said diabetes is Type 2 diabetes.

12. A method of identifying a compound which inhibits or negatively alters the function of a kinase, wherein said kinase causes IRS-1 degradation and reduces insulin signaling in an insulin-resistant cell,  
5 comprising contacting said test compound with said kinase for a time and under conditions sufficient for complexes to form between said test compound and said kinase, presence of said complexes indicating a compound which inhibits or negatively alters said function of said  
10 kinase.

13. A method of identifying a compound which inhibits or negatively alters the function of a phosphatase, wherein said phosphatase causes IRS-1  
15 degradation and reduces insulin signaling in an insulin-resistant cell, comprising contacting said test compound with said phosphatase for a time and under conditions sufficient for complexes to form between said test compound and said phosphatase, presence of said complexes  
20 indicating a compound which inhibits or negatively alters said function of said phosphatase.

14. A method of reducing or inhibiting IRS-1 degradation and increasing insulin-induced  
25 phosphorylation of PKB in a mammal in need of said reduction or inhibition of IRS-1 degradation and increased insulin-induced phosphorylation of PKB comprising administering to said mammal an siRNA against a kinase, wherein said kinase is selected from the group  
30 consisting of S6KB2, IKK2, PKC theta, pim 2, pyruvate dehydrogenase, PKC iota, PKC delta, UDP-N-acetylglucosamine-2-epimerimase/N-acetylmannosamine,

CaMKI-like protein, DAPK2, casein kinase 1 delta, casein kinase 1 gamma 3, DCAMKL1, SnK Akin kinase, NP\_067675, STK10, MAGUK p55 member 2, oxidative-stress responsiveness 1, NP\_060189, inositol 1, 3, 4 triphosphate 5-6 kinase, mitogen-activated protein kinase 4, mitogen-activated protein kinase 7, LIM kinase 2 (isoform 2b), phosphorylase kinase alpha 2, salt-inducible protein kinase, Jun kinase 1, 2, dystrophia myotonica protein kinase, CGPK1, MKK6, serine-threonine protein kinase PRP4 homolog, STE-2-like kinase, protein tyrosine kinase 9, P38 delta and adenylate kinase 3 (alpha-like) in an amount sufficient to effect said reduction or inhibition of IRS-1 degradation and increased insulin-induced phosphorylation of PKB.

15. The method of claim 14 wherein said mammal is selected from the group consisting of a human, a domesticated animal and a non-domesticated animal.

16. A method of reducing or inhibiting IRS-1 degradation and increasing insulin-induced phosphorylation of PKB in a mammal in need of said reduction or inhibition of IRS-1 degradation and increased insulin-induced phosphorylation of PKB comprising administering to said mammal an siRNA against a phosphatase, wherein said phosphatase is PTEN, in an amount sufficient to effect said reduction or inhibition of IRS-1 degradation and increased insulin-induced phosphorylation of PKB.

17. The method of claim 16 wherein said mammal is

selected from the group consisting of a human, a domesticated animal and a non-domesticated animal.

18. A method of decreasing IRS-1 degradation and increasing insulin-induced phosphorylation of PKB in a mammal in need of said decrease of IRS-1 degradation and increased insulin-induced phosphorylation of PKB comprising administering to said mammal an agonist of the kinase, wherein said kinase is selected from the group consisting of AXL, liver phosphofructokinase, death-associated kinase-3, galactokinase 1 and fyn-related kinase, in an amount sufficient to effect said reduced IRS-1 degradation and increased insulin-induced phosphorylation of PKB.

19. The method of claim 18 wherein said mammal is selected from the group consisting of a human, a domesticated animal and a non-domesticated animal.

20. A method of identifying a compound which increases activity of a kinase, wherein activity of said kinase prevents IRS-1 degradation, comprising contacting said test compound with said kinase for a time and under conditions sufficient for complexes to form between said test compound and said kinase, presence of said complexes indicating a compound which increases activity of said kinase.

21. The method of claim 20 wherein said kinase is selected from the group consisting of AXL, liver phosphofructokinase, death-associated kinase-3, galactokinase 1 and fyn-related kinase.